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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/471,523	12/23/1999	Richard B. van Breemen	21726/90386	7519

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BARNES & THORNBURG
P.O. BOX 2786
CHICAGO, IL 60690-2786

EXAMINER	
TRAN, MY CHAU T	
ART UNIT	**PAPER NUMBER**
1639	25

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/471,523	Applicant(s) VAN BREEMEN ET AL.	
	Examin r My-Chau T. Tran	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-30* is/are pending in the application.

4a) Of the above claim(s) *24-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-23 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Note: The examiner for your application in the PTO has changed. However, the Group and/or Art Unit location of your application in the PTO is remained the same, which is Group Art Unit 1639.

1. Applicant's amendment filed 12/3/02 in Paper No. 21 is acknowledged and entered. Claims 1-5 and 7-12 are canceled by the amendment. Claims 13-29 are added by the amendment.

2. Applicant's amendment filed 6/25/03 in Paper No. 24 is acknowledged and entered. Claims 13, 17-19, 21, and 23-24 are amended by the amendment. Claim 30 is added by the amendment.

3. Claims 13-30 are pending.

Election/Restrictions

4. As stated in the previous Office action (Paper No. 22) since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 24-29 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The requirement is still deemed proper and is therefore made **FINAL**.

5. The previous rejections 35 USC 112, first paragraph (new matter), for claims 13-23 have been withdrawn in view of applicant's amendments of claim 21 and arguments comparing the presently amended claims and the original claims.

6. The previous rejections 35 USC 112, second paragraph, for claims 13-22 have been withdrawn in view of applicant's amendments of claims 13, 17-19, and 21.

7. Applicant's arguments with respect to the rejection under 35 USC 112, first paragraph (written description), for Claims 13-23 have been considered but are moot in view of the new ground(s) of rejection.

8. Claims 13-23 and 30 are treated on the merit in this Office Action.

New Rejections

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 13-23, and 30 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

These claims encompass a broad genus of compounds or mixture of compounds and the products produce from its reaction with a broad genus of the biological material. For example, claim 13 outlines the method steps of screening ***any*** compounds or mixture of compounds for its biological activity wherein the method steps comprise of (a) providing an ultrafiltration chamber with a supportive solution "that facilitates reactions between the biological material and the compound or the mixture of compounds to produce products of the reactions" (b) filtering out the product of the reactions and (c) "analyzing the product of the reactions to determine whether the compound or any of the mixture of compounds is suitable for use as a drug or natural product." The scope of this claimed "screening" method includes an infinite number of compounds or mixture of compounds with an infinite number of structural variants (i.e., drug such as tricyclic antidepressants, steroids, and anticholingerics or natural products such as plants) wherein no distinguishing structural attributes are provided for the members of either the "compounds" or "mixture of compounds". Additionally, the interaction (e.g. functionality) of the compounds or mixture of compounds with any biological material, and product of a desired reaction would depend on the type of functional group(s) on the compounds or mixture of compounds. Therefore, the limitation of step (c) of "providing a continuous flow of a supportive solution to the ultrafiltration chamber that facilitates reactions between the biological material and the compound or the mixture of compounds to produce products of the reactions" would not provide ***any*** guidance as to the structure of the compounds or mixture of compounds. The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the compounds or mixture of compounds. Although the specification discloses many possible compounds or mixture of

compounds that "might" be "screened" by this method (see Specification, pages 16-19), the specification and claims do not provide ***any*** guidance as to what structural features ***all*** of these compounds or mixture of compounds share. Consequently, it is not possible to determine *a priori* which compounds or mixture of compounds would encompass because there is no common structural attributes that can link together ***all*** of these potential compounds or mixture of compounds i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* ***all*** the different types of compounds that should be included in this genus from the few examples provide by applicants.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, listing examples like pentoxyresorufin, imipramine, and chlorpromazine (see specification, examples, pages 16-17) is insufficient to teach the entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 13-22 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Clarification is needed for the order of the method steps of claim 13, since it is unclear with regard to step (c) of "providing a continuous flow of a supportive solution to the ultrafiltration chamber that facilitates reactions between the biological material and the compound or the mixture of compounds to produce products of the reactions" if the compounds or mixture of compounds of step (b) passes through the membrane of the ultrafiltration chamber (i.e. the ultrafiltration chamber of step (a) is the same as the ultrafiltration chamber of step (b)).

b) It is unclear in claim 13 with regard to "maintaining" the compounds or mixture of compounds in the ultrafiltration chamber in order for it to react with the biological material.

c) Claim 19 recites the limitation "suitable condition" in line 1 and "ultrafiltration membrane" in line 2. There is insufficient antecedent basis for this limitation in the claim 13.

d) It is unclear as to the correlation of the concentrations of small molecules of claim 30 to the determination of "cellular permeability or absorption" if the small molecules are the products of the reaction between the biological material and the compound or the mixture of compounds of claim 21. That is cellular uptake ("cellular permeability or absorption") would not produce a "product" that would be filtered for the membrane "will not allow passage of the biological material out of the chamber".

e) Claim 22 recites the limitation "multiple chambers" in line 1. There is insufficient antecedent basis for this limitation in the claim 13.

13. Claims 13-22 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: It is unclear as to the correlation of analyzing the product of the reactions between the biological material and the compound or the mixture of compounds and determining that the compound or the mixture of compounds is suitable for use as a drug or natural product compound. For example, the compound is a library of oligonucleotides and the biological material is DNA the resulting product is a hybridization of DNA. Therefore, it is unclear as to the correlation of the analysis of the resulting hybridization and the determination that the library of oligonucleotides is suitable for use as a drug or natural product compound.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

15. Claims 13-21 are rejected under 35 U.S.C. 102(b) as being anticipated by van Breemen et al. (*Analytical Chemistry*, **06/01/1997**, 69(11):2150-2164).

Van Breemen et al. disclose a method of on-line combination of ultrafiltration and electrospray mass spectrometry, which facilitates the identification of solution-phase ligands in library mixtures that bind to solution-phase receptors (Abstract; pg. 2159, right col., lines 8-14). The method steps comprise of placing the enzymes (biological materials) and a library of adenosine analogs (compounds) into the ultrafiltration chamber by injection (pg. 2160, right col., lines 18-38; pg. 2161, left col., lines 25-39; pg. 2163, left col., lines 9-26; fig. 1). The compounds is allowed to react with the enzymes to form a ligand-receptor complex. The ultrafiltration chamber comprise of a membrane that only allow low molecular weight solution-phase compound to pass through (fig. 1; pg. 2161, left col., lines 25-39). After the unbound library of compounds is wash away, the ligand-receptor complex is disrupted so that the ligand is release into the mass spectrometer for identification (pg. 2161, left col., lines 25-39; pg. 2163, left col., lines 9-26; fig. 1). Therefore, the method of van Breemen et al. anticipates the presently claimed method.

16. Claims 13-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhao et al. (*J. Med. Chem.*, **12/05/1997**, 40(25):4006-4012).

Zhao et al. disclose a method of on-line combination of ultrafiltration and electrospray mass spectrometry, which facilitates the identification of solution-phase ligands in library mixtures that bind to solution-phase receptors (Abstract; pg. 4006, right col., lines 1-19). The method steps comprise of placing the enzymes (biological materials) and a library of adenosine analogs (compounds) into the ultrafiltration chamber by injection (pg. 4007, left col., lines 12-23; pg. 4011, right col., lines 59-76 to pg. 4012, left col., lines 1-17; fig. 1). The compounds is allowed to react with the enzymes to form a ligand-receptor complex. The ultrafiltration chamber comprise of a membrane that only allow low molecular weight solution-phase compound to pass through (fig. 1; pg. 4011, right col., lines 59-76 to pg. 4012, left col., lines 1-17). After the unbound library of compounds is wash away, the ligand-receptor complex is disrupted so that the ligand is release into the mass spectrometer for identification (pg. 4011, right col., lines 59-76 to pg. 4012, left col., lines 1-17; fig. 1). Therefore, the method of Zhao et al. anticipates the presently claimed method.

17. Claims 13-21, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Venton et al. (US Patent 5,366,862).

Venton et al. disclose a method of screening a library of peptides (mixture of compounds) for peptides with high binding affinity for a target, "trapping" the binding complex form, and analyzing the binding complex (Abstract; col. 9, lines 33-63). The target is a macromolecule or

macromolecular complex such as enzymes (col. 14, lines 15-63). The binding complex is "trapped" by a semi-permeable membrane that allows the free passages of the peptides and not the target or binding complex (col. 15, lines 33-44). The apparatus use for the "trapping" of the binding complex comprises multiple compartments divided by the semi-permeable membrane in order to perform parallel binding assay (col. 15, lines 33-38; col. 16, lines 45-56). Buffer solutions (supportive solution) are added in the "trapping" chamber in order to assist in the binding reaction (col. 18, lines 36-49). Therefor the method of Venton et al. anticipates the presently claimed invention.

18. Claims 13-21, and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Venton et al. (US Patent 5,872,015).

The applied reference has a common inventor (e.g. Richard B. van Breemen) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Venton et al. disclose a method for the identification, concentration and isolation of a chemical compound from a mixture of compounds on the basis of the binding affinity of the chemical compound to a macromolecule or complex thereof, that is, to a receptor (Abstract; col. 3, lines 18-38; col. 4, lines 40-52). Both the compounds to be assayed and the macromolecules to which the compounds may bind are free in solution. The method comprises contacting a

mixture of compounds in solution with a solution of macromolecules or complexes thereof in a device possessing an ultrafiltration membrane to retain the receptor and bound compound receptor complex; washing through the device non-bound compounds; and releasing a bolus of the bound compound which passes through the ultrafiltration membrane where it may be analyzed chemically and/or spectrally (e.g. mass spectrometry) and/or bioassayed (col. 9, lines 13-60). The compounds libraries include many different compounds such as peptides and polysaccharides (col. 18, lines 61-67 to col. 19, lines 1-16). The macromolecule includes many different type of receptors such enzymes and DNA (col. 19, lines 43-67 to col. 20, lines 1-55). Therefore the method of Venton et al. anticipates the presently claimed method.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 13-23, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Venton et al. (US Patent 5,366,862) and Venton et al. (US Patent 5,872,015). *Note: Venton et al. #1 is (US Patent 5,366,862) and Venton et al. #2 is (US Patent 5,872,015).*

Venton et al. #2 disclose a method for the identification, concentration and isolation of a chemical compound from a mixture of compounds on the basis of the binding affinity of the chemical compound to a macromolecule or complex thereof, that is, to a receptor (Abstract; col. 3, lines 18-38; col. 4, lines 40-52). Both the compounds to be assayed and the macromolecules to which the compounds may bind are free in solution. The method comprises contacting a mixture of compounds in solution with a solution of macromolecules or complexes thereof in a device possessing an ultrafiltration membrane to retain the receptor and bound compound receptor complex; washing through the device non-bound compounds; and releasing a bolus of the bound compound which passes through the ultrafiltration membrane where it may be analyzed chemically and/or spectrally (e.g. mass spectrometry) and/or bioassayed (col. 9, lines 13-60). The compounds libraries include many different compounds such as peptides and polysaccharides (col. 18, lines 61-67 to col. 19, lines 1-16). The macromolecule includes many different type of receptors such enzymes and DNA (col. 19, lines 43-67 to col. 20, lines 1-55).

The method of Venton et al. #2 does not expressly disclose that the ultrafiltration chamber comprise of multiple chambers with ultrafiltration membranes arranged in parallel.

Venton et al. #1 disclose a method of screening a library of peptides (mixture of compounds) for peptides with high binding affinity for a target, "trapping" the binding complex form, and analyzing the binding complex (Abstract; col. 9, lines 33-63). The target is a

macromolecule or macromolecular complex such as enzymes (col. 14, lines 15-63). The binding complex is "trapped" by a semi-permeable membrane that allows the free passages of the peptides and not the target or binding complex (col. 15, lines 33-44). The apparatus use for the "trapping" of the binding complex comprises multiple compartments divided by the semi-permeable membrane in order to perform parallel binding assay (col. 15, lines 33-38; col. 16, lines 45-56). Buffer solutions (supportive solution) are added in the "trapping" chamber in order to assist in the binding reaction (col. 18, lines 36-49).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include in the ultrafiltration chamber multiple chambers with ultrafiltration membranes arranged in parallel as taught by Venton et al. #1 in the method of Venton et al. #2. One of ordinary skill in the art would have been motivated to include in the ultrafiltration chamber multiple chambers with ultrafiltration membranes arranged in parallel in the method of Venton et al. #2 for the advantage of provide screening for binding target any of a plurality of targets (Venton et al. #1: col. 16, lines 55-56) since both Venton et al. #1 and Venton et al. #2 disclose the same type of ultrafiltration chamber (Venton et al. #1: col. 15, lines 33-44; Venton et al. #2: col. 3, lines 18-38; col. 4, lines 40-52).

However, based on the disclosure of methods of screening compounds that have high binding affinity to a target in these references (Venton et al. #1 and Venton et al. #2), it would be obvious to one skilled in the art at the time the invention to formulate and dispense the reagents used in the method of screening compounds that have high binding affinity to a target in a kit of claim 23 for ease of use.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to My-Chau T. Tran whose telephone number is 703-305-6999. The examiner is on Increased Flex Schedule and can normally be reached on Monday: 8:00-2:30; Tuesday-Thursday: 7:30-5:00; Friday: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang can be reached on 703-306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

mct
September 21, 2003

PADMASHRI PONNALURI
PRIMARY EXAMINER